

WHAT IS CLAIMED IS:

1. An apparatus for manipulating cells comprising:

a plate having wells which hold cells:

a controller; and

a pipette means for aspirating a well and controlled by the controller which guides the pipette means to a predetermined position in a well of the plate having a predetermined cell to aspirate the cell with the pipette from the well and place it at another location.

2. An apparatus as described in Claim 1 wherein the aspirating means aspirates a population of cells or a subpopulation of a larger set of cells from the well and moves them to another location.

436/92 3. A method for analyzing cells comprising the steps of:

placing cells in a solution having a methyl cellulose concentration on a plate having between 6 and 9,600 wells with corresponding volumes of approximately 1 to 4% of the total volume of the solution; and

imaging a first well of the plate by visible light tracking; taking pictures of a second well of the plate; tracking a third well of the plate by fluorescence, and taking a focal stack of a fourth well of the plate to review 3D motion in the fourth well.

of: (4) A method for analyzing cells comprising the steps

imaging at least one cell in a first well of a plate with viable light to form a first image;

imaging the cell in the well by fluorescent light to form a second image; and

overlaying the first and second images.

(5) A method as described in Claim 4 including the step of taking successive fluorescent images over time and analyzing the successive images to determine cellular performance.

(6) A method as described in Claim 4 including the step of taking successive visible images over time and analyzing the successive images to determine cellular performance.

(7) A method as described in Claim 4 including the step of taking multiple visible and fluorescent images over time and overlaying them on one another and difference between successive overlaid images are analyzed to determine cellular performance.

(8) A method as described in Claim 5 including the steps of taking differences between the images and analyzing them to produce time related kinetic information on cellular performance.

(9) A method as described in Claim 6 wherein the kinetic information on cellular performance includes information on the effect of proteins and/or other biological or chemical moieties on cellular performance.

Sub A2 ^{10.} ~~determining~~ A method as described in Claim 7 wherein the measurement of cellular performance include the parameters as listed in Table 1.

11. A method as described in Claim 8 wherein the measurement of cellular performance is performed based upon a statistical analysis of time-related and kinetic parameters.

12. An apparatus for housing cells comprising:

a container having a plate with a plurality of wells in which cells reside;

means for maintaining a desired humidity in the wells, the maintaining means in contact with the plate and disposed over the wells; and

means for transferring fluid to each well while the maintaining means is in contact with and disposed over the wells.

13. An apparatus as described in Claim 4 wherein the maintaining means also diffuses light passing into the wells.

14. An apparatus as described in Claim 5 wherein the maintaining means includes filter paper.

15. An apparatus as described in Claim 5 wherein the maintaining means includes a gel lid.

16. An apparatus as described in Claim 7 wherein the transferring means includes a needle.

Sub A3 17. An apparatus for housing cells comprising:

a container having a plate with a plurality of wells in which cells reside; and

means for introducing to and removing fluids from each well, the introducing means includes a syringe to introduce liquids into and out of a well, vials which hold desired liquids, and a valve to direct fluids to the vials and paths the cells in the wells.

18. An apparatus as described in Claim 17 including means to maintain a less than 21% oxygen concentration in the container.

19. An apparatus as described in Claim 17 wherein the syringe includes at least one needle in operative relationship with the wells; the introducing means includes a controller to control the syringe; and including a station for cleaning the needle and removing waste from the container.

20. An apparatus as described in Claim 19 wherein the controller causes the needle to stain a cell in a well when the cell experiences a predetermined event.

21. An apparatus as described in Claim 19 wherein the predetermined biological event includes any of the parameters listed in Table 1.

22. An apparatus as described in Claim 20 wherein the controller causes the needle to add or remove liquid from a well at a specified time due to a cellular or biological event in the well.

23. An apparatus as described in Claim 22 wherein the syringe includes a second needle which removes fluid from a well in the plate and the needle dispenses fluid into a well in the plate.

24. An apparatus as described in Claim 22 wherein the syringe includes a first tube and a second tube connected to the needle, wherein the first tube dispenses fluid through the needle to the well in the plate and the second tube removes fluid from the well in the plate through the needle.

25. An apparatus for aligning light in a well of a plate or holding cells comprising:

a top portion that is adapted to hold to the plate; and

a bottom portion connected to the top portion that is adapted to extend into the well below a meniscus in the well, the top and bottom portions made of a transparent material which lets light pass through it and be distributed evenly throughout the bottom of the well.

26. An apparatus as described in Claim 25 wherein the top and bottom portion has a channel extending through them for a needle to pass through the channel and access the bottom of the well.

27. An apparatus as described in Claim 26 including at least a second portion extending from the top portion and adapted to be disposed in a second well of the plate.

28. A method for determining a condition of a cell comprising the steps of:

1.003361.103301

placing a bead coated with a first material in a well of a plate; and

identifying a second material released by a cell in the well by the second material reacting with the first material.

29. A method as described in Claim 28 wherein the identifying step includes the step of staining the bead with a stain that identifies when the second material reacts with the first material.

30. A method as described in Claim 29 including the step of coating the bead with the first material.

31. An apparatus for indicating a condition of a cell comprising:

a bead; and

a layer of a first material that reacts with a second material that is released from the cell when it is the condition, the layer coating the bead.

32. A method for lighting a well comprising the steps of:

placing a top portion of a light alignment apparatus onto a plate having wells so a bottom portion of the light alignment apparatus extends into a well and below a meniscus in the well; and

directing light onto the top portion that is evenly distributed by the bottom portion to the bottom of the well.

40032664.102601

taking images at focal points above a current setting
and below the current setting; and

34. A method as described in Claim 33 wherein the focusing bead step includes the steps of focusing on each bead visibly, focusing on each bead using fluorescence of the bead, and using that information to determine the proper focus for that well.

36. A method as described in Claim 35 including the step of storing the focus profile.

37. A method is described in Claim 36 including the step of determining that a second plate is a same type the plate that has previously had a focus profile identified; and reusing the focus profile that has been stored with the plate with the second plate.

38. A method as described in Claim 37, including the step of moving to three positions on the second plate; and transforming previous positions stored of the plate to new locations on the second plate.

39. A method for manipulating cells comprising the steps of:

guiding a pipette with a controller to a predefined position in a well of a plate having a predetermined cell;

aspirating the cell with the pipette from the well; and

placing the cell at another location with the pipette at the guidance of the controller.

40. A method as described in Claim 39 wherein the placing step includes the step of placing the cell in another well of the plate.

41. A method as described in Claim 40 wherein the placing step includes the step of placing the cell in a container disposed outside the plate.

42. A method for monitoring cells comprising the steps of:

loading one cell in each well of a plurality of wells of a plate; and

causing each cell to move to a corner of each well.

43. A method as described in Claim 42 including after the causing step, there is the step of locating each cell in each well with a microscope.

44. A method as described in Claim 43 wherein the causing step includes the step of tilting the plate.

10033661.102601

45. A method as described in Claim 43 wherein the causing step includes the step of centrifuging the plate.

46. A method as described in Claim 43 wherein the causing step includes the step of tilting the microscope.

47. A method as described in Claim 43 wherein the locating step includes the step of presetting focus of the microscope to the corner of each well.

48. A method for locating a cell in a well of a plate comprising the steps of:

placing a bead in each well of the plate; and

focusing a microscope on the bead in each well to facilitate the focus of the microscope on the cell in each well.

49. A method as described in Claim 48 wherein the focusing bead step includes the steps of focusing on each bead visibly, focusing on each bead using fluorescence of the bead, going to each corner of each well, and performing multiple object tracking on the cell in the corner.

50. A method as described in Claim 49 wherein after the locating step, there is the step of removing each well from scanning where no cell is detected.

51. A method as described in Claim 43 wherein the locating step includes the step of taking a focal stack of a position in at least one well.

10032661-102601

52. A method as described in Claim 43 wherein the locating step includes the step of imaging each well based on predetermined times or predetermined events.

53. An apparatus for monitoring cells comprising:

a plate having wells in which cells are disposed; and

means for causing each cell to move to a corner of each well, the causing means connected to the plate.

54. An apparatus as described in Claim 53 wherein the causing means includes a tilting mechanism for tilting the plate.

55. An apparatus as described in Claim 54 wherein the causing means includes an incubator that spins the plate, said plate in contact with the incubator.

56. An apparatus as described in Claim 55 including a microscope that locates each cell in each well.

57. An apparatus as described in Claim 56 including a microscope tilting mechanism that tilts the microscope.

58. An apparatus as described in Claim 57 including means for presetting focus of the microscope to the corner of each well.

59. An apparatus as described in Claim 58 including beads disposed in the wells.

1003364.103601